IMGN779: A CD33-TARGETED ANTIBODY-DRUG CONJUGATE (ADC) UTILIZING A NOVEL DNA ALKYLATOR, DGN462, IS HIGHLY ACTIVE IN VITRO AGAINST PRIMARY PATIENT AML CELLS AND IN VIVO AGAINST AML XENOGRAFTS IN MICE

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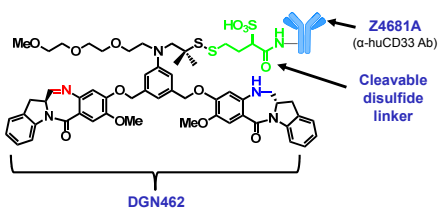
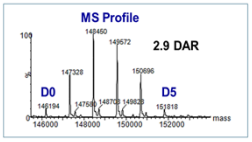
BACKGROUND: Despite high initial response rates (about 80%) to chemotherapy, many patients with acute myeloid leukemia (AML) experience a relapse of the disease, thought to be due to the outgrowth of persistent leukemic stem cells (LSC). The differential expression of CD33 on LSC compared to normal hematopoietic stem cells (HSC) makes CD33 an attractive target for treatment of AML with a CD33-targeted antibody-drug conjugate (ADC).

We have developed a new, highly potent DNA alkylator, DGN462, which consists of an indolino-benzodiazepine dimer containing a mono-imine moiety. IMGN779 is an ADC comprising DGN462 conjugated to the anti-huCD33 antibody, Z4681A, via a cleavable disulfide linker.

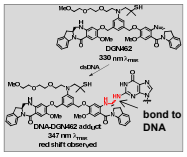
IMGN779 Structure & Biochemical Characteristics



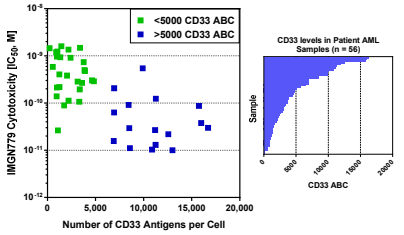


- ~3 DGN462 molecules conjugated per antibody
- Symmetrical mass distribution profile, very low unconjugated Ab (D0)

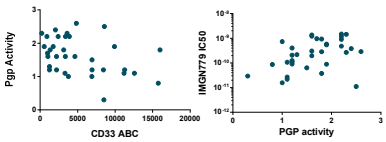
DGN462 Mechanism of Action



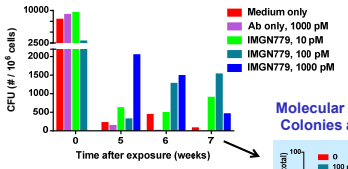
IMGN779 Demonstrates Highly Potent and CD33 Specific In Vitro Cytotoxicity Against Primary Patient AML Cells



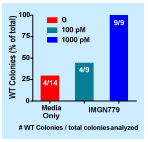
- Short-term liquid culture assay
- Highest IMGN779 activity generally observed with CD33 expression levels > 5000 antigens per cell.
- IMGN779 activity was CD33-specific. Non-targeted DGN462-ADC was not active (no IC_{50} reached at highest dose tested in 33/35 samples).
- CD33 levels ranged from ~200 to 16,000 antigens per cell.
- Pgp activity inversely correlated with CD33-expression levels and IMGN779 cytotoxicity



IMGN779 Causes a Dose-Dependent Decrease of Leukemic Colony Formation and Increase in Normal HSC Colonies in Long-Term LSC Cultures

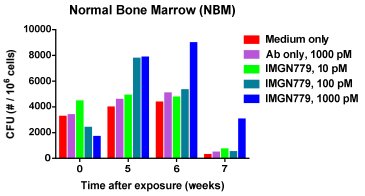


Molecular Analysis of Colonies at 7 Weeks



- IMGN779 eliminates LSCs
- Surviving colonies (wild-type, WT) are derived from normal HSCs.
- Increased colony formation was also observed in long-term cultures of NBM after treatment with IMGN779, indicating that HSCs are spared.

Normal Bone Marrow (NBM)



AML Cell Lines are Highly Sensitive to IMGN779 and DGN462

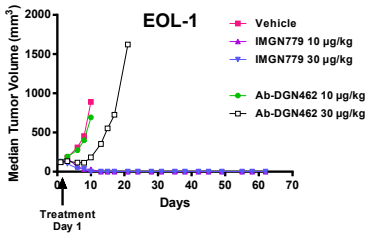
Cell Line	CD33 ABC	DGN462 IC_{50} (pM)	IMGN779 IC_{50} (pM)
OCI-AML3	1532	10	300
KASUMI-1	3727	600	3000
EOL-1	7864	10	10
MV4-11	17757	5	2
HL60/QC	21000	30	16
OCI-M1	55353	100	20

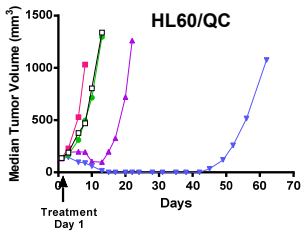
Subset of results from the panel of 21 cell lines tested

A panel of 21 AML cell lines were evaluated in vitro:

- CD33 expression ranged from 1,000 – 55,000 antigens per cell
- DGN462-SMe (free drug) median IC_{50} =38 pM (5 to 3900 pM)
- IMGN779 median IC_{50} = 70 pM (2 to 3000 pM IC_{50})

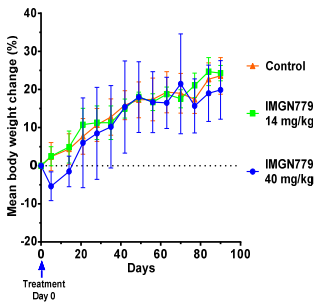
IMGN779 Is Highly Active and Antigen Specific Against Human AML Xenografts at a Minimally Efficacious Dose of 0.6 mg/kg





Model	ADC	DGN462 (µg/kg)	Ab (mg/kg)	T/C (%)	CR	Result
EOL-1	IMGN779	10	0.6	3	5/6	highly active (MED)
		30	1.8	0	6/6	highly active
	Nontargeting Ab-DGN462	10	0.4	78	0/6	inactive
		30	1.3	20	1/6	active
HL60/QC	IMGN779	10	0.6	19	1/6	active (MED)
		30	1.8	9	6/6	highly active
	Nontargeting Ab-DGN462	10	0.4	48	0/6	inactive
		30	1.3	46	0/6	inactive

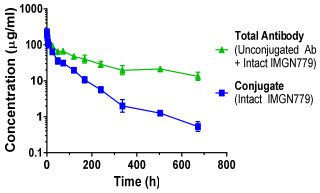
IMGN779 is Well Tolerated in CD-1 Mice: No Hepatotoxicity or Delayed Toxicity

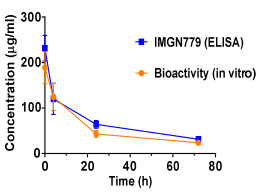


Toxicology Assessment

- IMGN779 does not cause liver toxicity in mice at the MTD dose.
- ALT/AST values were comparable to normal reference ranges for CD-1 mice.
- No evidence of delayed toxicity that is observed with ADCs containing DNA-crosslinking agents

IMGN779 has Pharmacokinetic Profile and In Vivo Stability Comparable to ADCs with Cleavable Linkers: Conjugate Bioactivity is Maintained for at Least 3 Days





Assay	t1/2 (h)	t1/2 (d)	Cmax (µg/mL)	CL (mL/hr/kg)	Vss (mL/kg)
Total Ab	258	10.8	223	0.2	69
Conjugate	80	3.3	231	0.7	67

IMGN779 demonstrates highly potent, CD33-targeted activity against AML cell lines, primary patient AML cells, and human AML xenografts with a favorable safety profile, supporting its advancement as a potential treatment for AML which may confer a therapeutic advantage over existing clinical agents